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10/566,266	05/16/2008	Reiko Matsuyama	MATSUYAMA1	1891

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EXAMINER	
TSAY, MARSHA M	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,266	MATSUYAMA ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-43* is/are pending in the application.

4a) Of the above claim(s) *37-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election with traverse of Group I, claims 23-36, to the species chicken β-actin promoter, dihydrofolate reductase (dhfr) gene, Chinese hamster ovary cells (CHO), in the reply filed on October 27, 2010 is acknowledged. The traversal is on the ground(s) that even if Roy et al. were interpreted to anticipate or make obvious the broadest presently pending claims (which it does not), there would still be common patentable subject matter existing in the recited groups, thereby meeting the requirements of a technical relationship between the groups of inventions involving one or more of the same or corresponding special technical features, as required by PCT Rules 13.1 and 13.2. The species election is traversed on the basis that the generic claims themselves define a single general inventive concept under PCT Rules 13.1 and 13.2 because such claims themselves recite the same or corresponding special technical features. This is not found persuasive because the reasons are noted in the restriction requirement of September 28, 2010.

The requirement is still deemed proper and is therefore made FINAL.

Claims 37-43 have been withdrawn from further consideration by the Examiner because they are drawn to non-elected inventions. Claims 23-36, to the species chicken β-actin promoter, dhfr gene, CHO cells, are currently under examination.

Priority: The request for priority to JAPAN 2004-096215, filed March 29, 2004, and JAPAN 2003-282033, filed July 29, 1993, is acknowledged. Certified copies of the foreign priority documents have not been included with the instant application's file.

Claim Objections

Claim 32 is objected to because of the following informalities: in claim 32, line 3, the "a" before α chain should be amended to "an". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing a recombinant fibrinogen producing cell which produces a high level of fibrinogen by incorporating into an animal cell, genes encoding an α chain, a β chain, and a γ chain, does not reasonably provide enablement for a process for producing a recombinant fibrinogen producing cell which produces a high level of fibrinogen by incorporating into an animal cell a gene encoding a variant of an α chain, a variant of a β chain, and a variant of a γ chain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art to ascertain which genes encoding variants of an α chain, a β chain, and a γ chain can be incorporated into an animal cell such said cell produces a high level of recombinant fibrinogen. Thus there could be thousands of variants which contain

substitutions, deletions, additions etc. Thus for the instant claimed invention, it would require an undue burden of experimentation for a skilled artisan to determine exactly which gene variants can successfully encode an α chain, a β chain, and a γ chain.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case the quantity of experimentation would be large since there are myriad substitutions, deletions or insertions to choose from. The amount of guidance in the specification is zero with regard to which genes can encode variants of an α chain, a β chain, and a γ chain at a high level. No working examples are present of an animal cell which produces a high level of fibrinogen, having genes encoding variants of an α chain, a β chain, and a γ chain. The nature of

the invention is such that genes encoding variants of an α chain, a β chain, and a γ chain may or may not encode high levels of recombinant fibrinogen that have biological activity. The state of the prior art is that even proteins that are 99% similar to the wild-type protein are at times not fully active. The relative level of skill in this art is very high. The predictability as to what substantially similar protein will have which activity is zero.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

Claims 23-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a process for producing a recombinant fibrinogen producing cell which produces a high level of fibrinogen by incorporating into an animal cell a gene encoding a variant of an α chain, a variant of a β chain, and a variant of a γ chain. Vas-Cath Inc. V. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now *claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." As stated above, genes encoding a variant of an α chain, a variant of a β chain, and a variant of a γ chain. However, the skilled artisan cannot necessarily envision the detailed structures of ALL of the genes encoding variants of an α

chain, β chain, and γ chain that produce a recombinant fibrinogen that has the same functional activity as a wild-type fibrinogen protein because nowhere in the specification is it described which amino acids are even essential and critical for the wild-type protein to maintain its functionality, and therefor conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods of making the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

Claim 23 recites a recombinant fibrinogen producing cell which highly produces fibrinogen. It is unclear if by "highly produces fibrinogen", the cell produces a "high level of fibrinogen." Additionally, it is unclear what amount and/or concentration would be considered a "high" level of fibrinogen.

Claims 23 and 24 recite that the number of a γ chain gene is 1- to 1000-fold amount of a total number of an α chain gene and a β chain gene. Applicants are asked to clarify this phrase because it is unclear what is the total number of said α chain gene and said β chain gene.

Regarding claims 25-29, it is unclear how the vectors recited in said claims are used by mixing them, i.e. are they mixed prior to incorporation into the animal cell, etc. Further clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-24, 29, 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited). For examination purposes, claim 23 has been interpreted as: a process for producing a recombinant fibrinogen producing cell which produces recombinant fibrinogen, wherein said process comprises incorporating into an animal cell, genes encoding an α chain, a β chain, and a γ chain.

Roy et al. disclose a method of making a recombinant fibrinogen producing cell which expresses fibrinogen protein comprising transfecting COS-1 cells with either pRSVNeo-Bβ, pRSVNeo-Aα, or pRSVNeo-γ or with combinations of equal amounts of two of these expression vectors, or with equal amounts of all three expression vectors (p. 4759; claims 23-24, 29, 32-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a recombinant fibrinogen producing cell that expresses fibrinogen protein by transfecting COS-1 cells with either pRSVNeo-Bβ, pRSVNeo-Aα, or pRSVNeo-γ or with combinations of equal amounts of two of these expression vectors, or with equal amounts of all three expression vectors as suggested by Roy et al. (claims 23-24, 29, 32-34). The motivation to do is given by Roy et al., which disclose the successful expression of recombinant fibrinogen by transfecting a COS-1 cell with expression vectors containing genes encoding fibrinogen chains, such that said COS-1 cell becomes a recombinant fibrinogen producing cell.

Claims 25-26, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited) in view of Lord et al. (1993 Blood Coagulation and Fibrinolysis 4(1): 55, abstract only). The teachings of Roy et al. are outlined above. Roy et al. do not teach that an expression vector encodes for more than one fibrinogen chain.

Lord et al. disclose that fibrinogen chains can be individually cloned into the same expression vector (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Roy et al. by cloning in combinations of two or three of the fibrinogen chains (selected from the α chain, the β chain, and the γ chain), into the same expression vector as suggested by Lord et al. and transfecting the animal cell with the combination of expression vectors such the transfected animal cell has an α chain, β chain, and γ chain gene present in said cell (claims 25-26, 28). The motivation to do is given by Lord et al. which disclose that genes

encoding fibrinogen chains can be cloned into the same expression vector; therefore, it would be reasonable for one of ordinary skill to determine which combination of vectors and fibrinogen genes would produce a high concentration of fibrinogen protein.

Claims 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited) in view of Lord (US 6037457). The teachings of Roy et al. are outlined above. Roy et al. do not teach CHO cells.

Lord discloses that recombinant fibrinogen can be expressed using CHO cells (col. 9-10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Roy et al. by substituting the CHO cells of Lord for the COS-1 cells used in Roy et al. (claim 35). The motivation to do is given by Lord, which discloses that CHO cells can also be used to successfully express recombinant fibrinogen. Regarding the claim 36, it should be noted that it would be well within the skill and knowledge of one of ordinary skill to determine which specific strain of CHO cells will express a high concentration of fibrinogen protein compared to other strains since different mammalian expression systems are known in the art. The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine which mammalian expression system will express a high concentration of fibrinogen protein. See also MPEP 2144.04-2144.05.

Claims 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roy et al. (1991 Journal of Biological Chemistry 266(8): 4758-4763; previously cited) in view of Lord (US 6037457) in view of Estes et al. (US 7423135). The teachings of Roy et al. in view of Lord are outlined above. Roy et al. in view of Lord do not teach chicken β-actin promoter and a dhfr gene.

Estes et al. disclose that chicken β-actin promoter can be employed with a dhfr gene in a suitable expression system for CHO cells (col. 7-11).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Roy et al. in view of Lord by substituting the chicken β-actin promoter and the dhfr gene of Estes et al. for the SV40 promoter and the Neo gene used in Roy et al. (claims 30-31). The motivation to do so is given by Estes et al., which disclose that chicken β-actin promoters are known in the art and can be used with the dhfr gene in a suitable expression system. It would be reasonable for one of ordinary skill to determine which combination of promoters and genes can be used with an animal cell to express a high concentration of fibrinogen protein. The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine which mammalian expression system will express a high concentration of fibrinogen protein. See also MPEP 2144.04-2144.05.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marsha M. Tsay/
Examiner, Art Unit 1656

January 3, 2011